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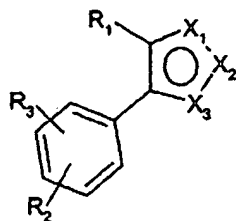
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(54) Title: PHENYL SUBSTITUTED TRIAZOLES AND THEIR USE AS SELECTIVE INHIBITORS OF AKL5 KINASE



(I)

(57) Abstract: Phenyl substituted triazoles of formula (I) wherein R1 is  
naphthyl or phenyl optionally substituted with one or more substituents  
selected from halo, -O-C1-6alkyl, -S-C1-6alkyl, C1-6alkyl, C1-6haloalkyl,  
-O-(CH2)<sub>n</sub>-Ph, -S-(CH2)<sub>n</sub>-Ph, cyano, phenyl, and CO2R, wherein R is  
hydrogen or C1-6alkyl, and n is 0, 1, 2 or 3; or R1 is phenyl or pyridyl fused  
with an aromatic or non-aromatic cyclic ring of 5-7 members wherein  
said cyclic ring optionally contains up to three heteroatoms, independently  
selected from N, O and S, and N may be further optionally substituted  
by C1-6 alkyl, and wherein the cyclic ring may be optionally substituted  
by =O; R2 and R3 are independently selected from H, C1-6alkyl,C1-6alkoxy, phenyl, NH(CH2)<sub>n</sub>-Ph, NH-C1-6alkyl, halo, alkoxy, CN, NO2, CONHR and SO2NHR; two of X1, X2 and X3 are N  
and the other is NR4 wherein R4 is hydrogen, C1-6alkyl, C3-7cycloalkyl, -(CH2)<sub>p</sub>-CN, -(CH2)<sub>p</sub>-CO2H, -(CH2)<sub>p</sub>-CONHR5R6,  
-(CH2)<sub>p</sub>-COR5, -(CH2)<sub>q</sub>(OR7)2, -(CH2)<sub>p</sub>OR5, -(CH2)<sub>q</sub>-CH=CH-CN, -(CH2)<sub>q</sub>-CH=CH-CO2H, -(CH2)<sub>p</sub>-CH=CH-CONHR5R6,  
-(CH2)<sub>p</sub>NHCOR8 or -(CH2)<sub>p</sub>NR9R10; R5 and R6 are independently hydrogen or C1-6alkyl; R7 is C1-6alkyl; R8 is C1-7alkyl,  
or optionally substituted aryl, heteroaryl, arylC1-6alkyl or heteroaryl C1-6alkyl; R9 and R10 are independently selected from  
hydrogen, C1-6alkyl, aryl and arylC1-6alkyl; p is 0-4; and q is 1-4 and salts and solvates thereof, are disclosed, as are methods for  
their preparation, pharmaceutical compositions containing them and their use in medicine.

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## PHENYL SUBSTITUTED TRIAZOLES AND THEIR USE AS SELECTIVE INHIBITORS OF ALK5 KINASE

This invention relates to phenyl substituted triazoles which are inhibitors of the transforming growth factor, ("TGF")- $\beta$  signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine.

TGF- $\beta$ 1 is the prototypic member of a family of cytokines including the TGF- $\beta$ s, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided in two classes, the type I or activin-like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF- $\beta$  signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF- $\beta$ , ALK5, in the presence of TGF- $\beta$ . The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. Generally it is believed that in many species, the type II receptors regulate cell proliferation and the type I receptors regulate matrix production. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production, and not the type II receptor mediated proliferation.

Activation of the TGF- $\beta$ 1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov. 10, 1994; 331(19):1286-92. Further, TGF- $\beta$ 1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF- $\beta$ 1 receptor ALK5. Zhang Y., Feng X.H., Derynck R., *Nature*, Aug. 27, 1998; 394(6696):909-13; Usui T., Takase M., Kaji Y., Suzuki K., Ishida K., Tsuru T., Miyata K., Kawabata M., Yamashita H., *Invest. Ophthalmol. Vis. Sci.*, Oct. 1998; 39(11):1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF- $\beta$ 1 has been implicated in many renal fibrotic disorders. Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov 10, 1994; 331(19):1286-92. TGF- $\beta$ 1 is elevated in acute and chronic glomerulonephritis, Yoshioka K., Takemura T., Murakami K., Okada M., Hino S., Miyamoto H., Maki S., *Lab. Invest.*, Feb. 1993; 68(2):154-63, diabetic nephropathy, Yamamoto, T., Nakamura, T., Noble, N.A., Ruoslahti, E., Border, W.A., (1993) *PNAS* 90:1814-1818, allograft rejection, HIV nephropathy and angiotensin-induced nephropathy, Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov. 10, 1994; 331(19):1286-92. In these diseases the levels of TGF- $\beta$ 1 expression coincide with the production

of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF- $\beta$ 1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF- $\beta$ 1 in vitro. Second, neutralizing anti-bodies against TGF- $\beta$ 1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF- $\beta$ 1 transgenic mice or in vivo transfection of the TGF- $\beta$ 1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., Factor V.M., Mozes M., Nagy P., Sanderson N., Bottinger E.P., Klotman P.E., Thorgeirsson S.S., *Lab Invest*, June 1996; 74(6):991-1003. Thus, inhibition of TGF- $\beta$ 1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF- $\beta$ 1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty, Saltis J., Agrotis A., Bobik A., *Clin Exp Pharmacol Physiol*, Mar. 1996; 23(3):193-200. In addition TGF- $\beta$ 1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF- $\beta$  receptor ALK5 correlated with total cholesterol ( $P < 0.001$ ) Blann A.D., Wang J.M., Wilson P.B., Kumar S., *Atherosclerosis*, Feb. 1996; 120(1-2):221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF- $\beta$  type II receptor ratio. Because TGF- $\beta$ 1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., Consigli S., Du B., Falcone D.J., Sanborn T.A., Spokojny A.M., Bush H.L., Jr., *J Clin Invest*, Dec. 1995; 96(6):2667-75. TGF- $\beta$ 1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodeling via a TGF- $\beta$ -dependent mechanism. Therefore, inhibiting the action of TGF- $\beta$ 1 on ALK5 is also indicated in atherosclerosis and restenosis.

TGF- $\beta$  is also indicated in wound repair. Neutralizing antibodies to TGF- $\beta$ 1 have been used in a number of models to illustrate that inhibition of TGF- $\beta$ 1 signaling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF- $\beta$ 1 and TGF- $\beta$ 2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., *J. Cell. Sci.*, 1995, 108, 985-1002. Moreover, TGF- $\beta$  antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., *Curr. Eye Res.*, 1998, 17, 736-747, and accelerate wound healing of gastric ulcers in the rat, Ernst H., *Gut*, 1996, 39, 172-175. These data strongly suggest that limiting the activity of TGF- $\beta$  would be beneficial in many tissues and suggest that any disease with chronic elevation of TGF- $\beta$  would benefit by inhibiting smad2 and smad3 signaling pathways.

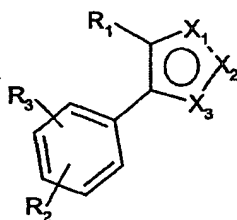
TGF- $\beta$  is also implicated in peritoneal adhesions Saed G.M., *et al*, *Wound Repair Regeneration*, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

TGFβ1-antibodies prevent transplanted renal tumor growth in nude mice through what is thought to be an anti-angiogenic mechanism Ananth S, *et al*, *Journal Of The American Society Of Nephrology Abstracts*, 9: 433A(Abstract). While the tumor itself is not responsive to TGF-β, the surrounding tissue is responsive and supports tumor growth by neovascularization of the TGF-β secreting tumor. Thus, antagonism of the TGF-β pathway should prevent metastasis growth and reduce cancer burden.

Surprisingly, it has now been discovered that a class of phenyl substituted triazoles function as potent and selective non-peptide inhibitors of ALK5 kinase and therefore, have utility in the treatment and prevention of various disease states mediated by ALK5 kinase mechanisms, such as chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis and restenosis.

Examples of diseases where fibrosis is a major component include, but are not limited to, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis.

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein R<sub>1</sub> is naphthyl or phenyl optionally substituted with one or more substituents selected from halo, -O-C<sub>1-6</sub>alkyl, -S-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, -O-(CH<sub>2</sub>)<sub>n</sub>-Ph, -S-(CH<sub>2</sub>)<sub>n</sub>-Ph, cyano, phenyl, and CO<sub>2</sub>R, wherein R is hydrogen or C<sub>1-6</sub>alkyl, and n is 0, 1, 2 or 3; or R<sub>1</sub> is phenyl or pyridyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms, independently selected from N, O and S, and N may be further optionally substituted by C<sub>1-6</sub> alkyl, and wherein the cyclic ring may be optionally substituted by =O;

R<sub>2</sub> and R<sub>3</sub> are independently selected from H, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, phenyl, NH(CH<sub>2</sub>)<sub>n</sub>-Ph, NH-C<sub>1-6</sub>alkyl, halo, CN, NO<sub>2</sub>, CONHR and SO<sub>2</sub>NHR;

two of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are N and the other is NR<sub>4</sub> wherein R<sub>4</sub> is hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-7</sub>cycloalkyl, -(CH<sub>2</sub>)<sub>p</sub>-CN, -(CH<sub>2</sub>)<sub>p</sub>-CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>p</sub>-CONHR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>p</sub>COR<sub>5</sub>,

$-(CH_2)_q(OR_7)_2$ ,  $-(CH_2)_pOR_5$ ,  $-(CH_2)_q-CH=CH-CN$ ,  $-(CH_2)_q-CH=CH-CO_2H$ ,  $-(CH_2)_p-CH=CH-CONHR_5R_6$ ,  $-(CH_2)_pNHCOR_8$  or  $-(CH_2)_pNR_9R_{10}$ ;

$R_5$  and  $R_6$  are independently hydrogen or  $C_{1-6}$ alkyl;

$R_7$  is  $C_{1-6}$ alkyl;

5  $R_8$  is  $C_{1-7}$ alkyl, or optionally substituted aryl, heteroaryl, aryl $C_{1-6}$ alkyl or heteroaryl $C_{1-6}$ alkyl;

$R_9$  and  $R_{10}$  are independently selected from hydrogen,  $C_{1-6}$ alkyl, aryl and aryl $C_{1-6}$ alkyl;

$p$  is 0-4; and

$q$  is 1-4.

10

In the triazole ring of the compounds of formula (I) it will be apparent that the double bond will be to the two unsubstituted nitrogens.

15 When  $R_1$  is pyridyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members the nitrogen of the pyridyl ring may be at the point of fusion. Preferably  $R_1$  is optionally substituted naphthyl or phenyl. More preferably  $R_1$  is phenyl optionally substituted with one or more substituents selected from halo,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkylthio, and phenyl; or  $R_1$  is phenyl or pyridyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms, independently selected from N, O and S, and N may  
20 be further optionally substituted by  $C_{1-6}$  alkyl, and wherein the cyclic ring may be optionally substituted by =O; for example  $R_1$  represents benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, quinoxalyl, dihydrobenzofuranyl, benzimidazolyl,  $C_{1-6}$  alkylbenzimidazolyl, [1,2,4]triazolo[1,5-a]pyridyl, benzo[1,4]oxazinyl-3-one, benzoxazolyl-2-one or benzo[1,4]oxazinyl. Most preferably  $R_1$   
25 represents 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-chlorophenyl, 3-fluoro-4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or  $R_1$  represents benzo[1,2,5]thiadiazolyl, [1,2,4]triazolo[1,5-a]pyridyl, dihydrobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzimidazolyl,  $C_{1-6}$  alkylbenzimidazolyl, benzo[1,4]oxazinyl-3-one or benzo[1,4]oxazinyl.

30 Preferably,  $R_2$  is positioned meta to the point of attachment to the triazole,  $R_2$  is preferably halo, e.g. chloro,  $C_{1-6}$  alkyl or  $NO_2$ . More preferably,  $R_2$  is halo.

$R_3$  is preferably hydrogen or halo.

35 The compounds for use in the methods of the invention preferably have a molecular weight of less than 800, more preferably less than 600.

Specific compounds of the invention which may be mentioned include the following and pharmaceutically acceptable salts thereof:

40 6-[5-(3-Chlorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine;  
6-[5-(3-Fluorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine;  
6-[5-(3-Nitrophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine;  
6-[5-(3-Methylphenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine;

- 6-[5-(4-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine;  
 6-[5-(4-Fluorophenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine;  
 6-[5-(4-Methylphenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine;  
 6-[5-(3,4-Difluorophenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine;  
 5 6-[5-(2-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine;  
 6-[5-(3-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one;  
 5-[5-(3-Chlorophenyl)-2*H*-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole;  
 5-[5-(3-Fluorophenyl)-2*H*-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole;  
 5-[5-(3-Bromophenyl)-2*H*-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole;  
 10 4-(3-Chlorophenyl)-5-(4-methoxyphenyl)-2*H*-[1,2,3]triazole;  
 4-(3-Fluorophenyl)-5-(4-methoxyphenyl)-2*H*-[1,2,3]triazole;  
 4-(3-Chlorophenyl)-5-(3-fluoro-4-methoxyphenyl)-2*H*-[1,2,3]triazole;  
 4-(3-Fluorophenyl)-5-(3-fluoro-4-methoxyphenyl)-2*H*-[1,2,3]triazole;  
 6-[5-(3-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-1-methyl-1*H*-benzoimidazole;  
 15 4-(3-Chlorophenyl)-5-(3-chloro-4-methoxyphenyl)-2*H*-[1,2,3]triazole; and  
 4-(3-Fluorophenyl)-5-(3-chloro-4-methoxyphenyl)-2*H*-[1,2,3]triazole.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate,  
 20 hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate and stearate.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes  
 25 within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention  
 30 includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical  
 35 compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably at least 10% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.  
 40

The term "C<sub>1-6</sub>alkyl" as used herein whether on its own or as part of a larger group e.g. C<sub>1-6</sub>alkoxy, means a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.

5

C<sub>1-6</sub>haloalkyl groups may contain one or more halo atoms, a particular C<sub>1-6</sub>haloalkyl group that may be mentioned is CF<sub>3</sub>.

10

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "cycloalkyl" as used herein means cyclic radicals, preferably of 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl and cyclohexyl.

15

The term "ALK5 inhibitor" as used herein means a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

20

The term "ALK5 mediated disease state" as used herein means any disease state which is mediated (or modulated) by ALK5, for example a disease which is modulated by the inhibition of the phosphorylation of smad 2/3 in the TGF- $\beta$ 1 signaling pathway.

25

The term "ulcers" as used herein includes but is not limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

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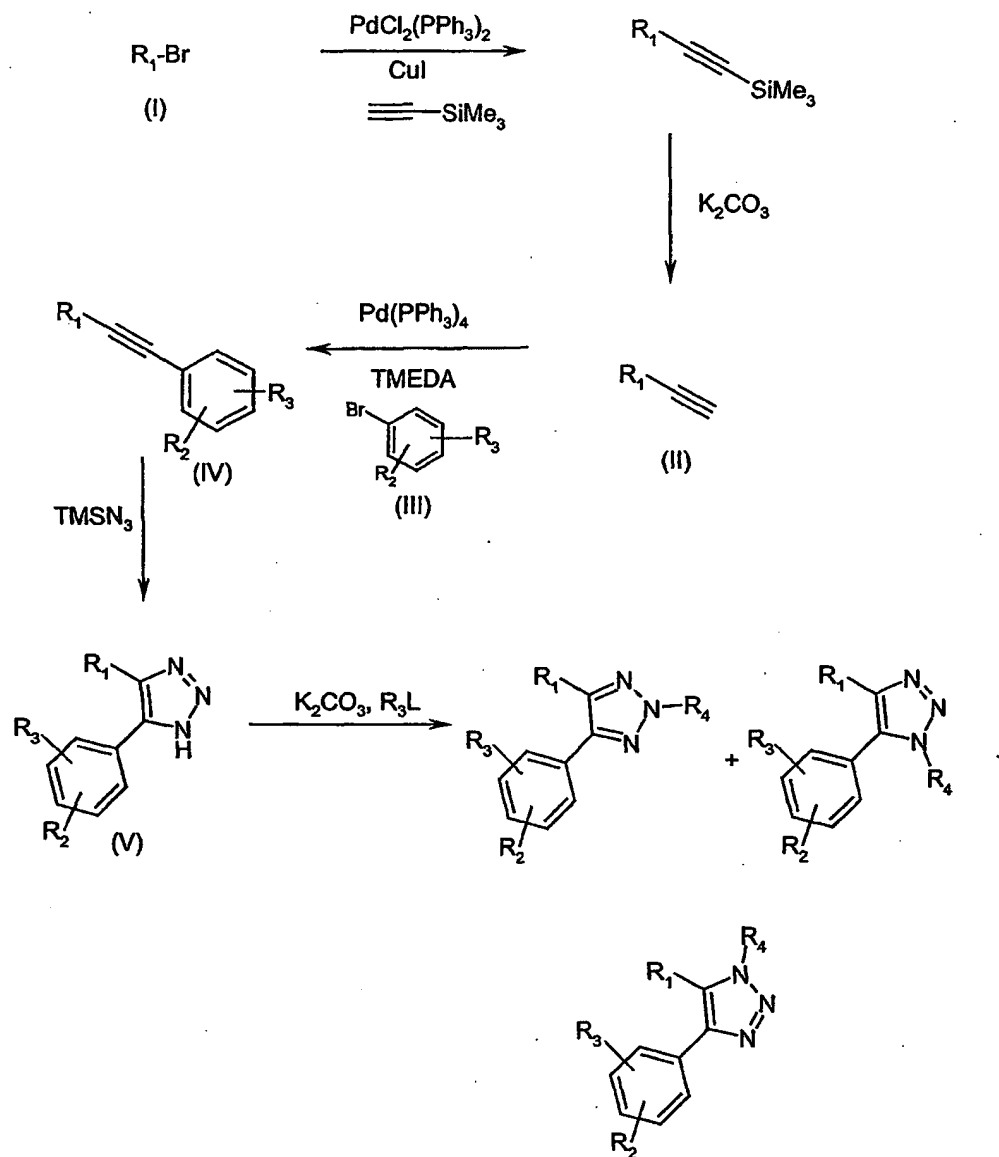
The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

35

Specifically, compounds of formula (I) may be prepared as illustrated in Scheme 1.

An aryl bromide (I) is coupled with trimethylsilylacetylene using a palladium catalyst in the presence of copper(I) iodide. The trimethylsilyl group is then removed under basic conditions with potassium carbonate and the unmasked terminal acetylene (II) is coupled to a substituted bromobenzene (III) via palladium catalysis. The disubstituted acetylene (IV) is treated with trimethylsilylazide to afford a triazole (V) which may be alkylated with a suitable alkylating agent, L-R<sub>3</sub> where L is a leaving group, e.g. I, in the presence of potassium carbonate. The resulting isomers can be separated by chromatographic methods.

Scheme 1



5

Further details for the preparation of compounds of formula (I) are found in the examples.

During the synthesis of the compounds of formula (I) labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

10



The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts thereof.

10 According to a further aspect of the present invention there is provided a method of treating a disease mediated by the ALK5 receptor in mammals, comprising administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 According to a further aspect of the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in therapy.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.

25 ALK5-mediated disease states, include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal abrasion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, and restenosis.

30 By the term "treating" is meant either prophylactic or therapeutic therapy.

According to a further aspect of the present invention there is provided a method of inhibiting the TGF- $\beta$  signaling pathway in mammals, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor, which method comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

40 According to a further aspect of the present invention there is provided a method of inhibiting matrix formation in mammals by inhibiting the TGF- $\beta$  signalling pathway, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor, which method comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) and pharmaceutically acceptable salts thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following examples are to be construed as merely illustrative and not a limitation on the scope of the invention in any way. In the Examples, mass spectra were performed using an Hitachi Perkin-Elmer RMU-6E with chemical ionization technique (CI) or a Micromass Platform II instrument with electrospray (ES) ionization technique.

5

**ABBREVIATIONS**

CuI – copper iodide

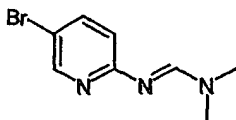
DMF - dimethylformamide

EtOAc – ethyl acetate

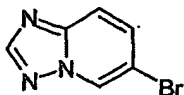
10 MgSO<sub>4</sub> – magnesium sulphateNaHCO<sub>3</sub> – sodium hydrogencarbonateNa<sub>2</sub>SO<sub>4</sub> – sodium sulphatePd(PPh<sub>3</sub>)<sub>4</sub> – tetrakis(triphenylphosphine) palladium(0)

THF – tetrahydrofuran

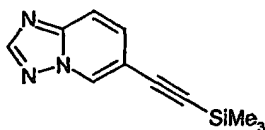
15 TMEDA – tetramethylethylenediamine

**Preparation 1: *N'*-(5-Bromo-2-aminopyridine)-*N,N*-dimethylformamidine**

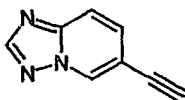
20 5-Bromo-2-aminopyridine (9.8 g, 56.6 mmol, 1 eq) was dissolved in dry DMF (20 ml) and dry dimethylformamide dimethylacetal (20 ml) under argon. The solution was refluxed at 130°C for 16 h, allowed to cool, and the solvents removed. The resultant residue was used in the next stage without purification; *m/z* [APCIMS]: 228.0/230.0 [*M*+*H*]<sup>+</sup>.

**25 Preparation 2: 6-Bromo-[1,2,4] triazolo[1,5-*a*] pyridine**

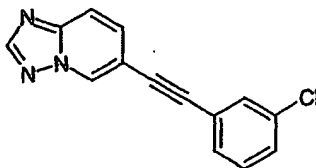
*N'*-(5-Bromo-2-aminopyridine)-*N,N*-dimethylformamidine (16.2 g, ~56.6 mmol, 1 eq) was dissolved in methanol (90 ml) and pyridine (10 ml) under argon and cooled down to 0°C. To this  
30 was added, with stirring, hydroxylamine-*O*-sulfonic acid (7.3 g, 75.2 mmol, 1.3 eq) to form a purple suspension. This was allowed to reach room temperature and stirred for 16 h. After removing the solvents, the residue was suspended in aqueous sodium hydrogen carbonate (200 ml) and extracted with ethyl acetate (2x200 ml). The organic layer was then washed with water and brine (100 ml of each), dried (MgSO<sub>4</sub>) and the solvent removed. Purification by flash  
35 chromatography on silica, eluting with a gradient solvent system of first 2:1 40-60°C petroleum ether:ethyl acetate to 1:1 40-60°C petroleum ether:ethyl acetate afforded the product as a pale yellow solid (5 g, 44.6%); <sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>) δ: 8.77 (1H, s), 8.34 (1H, s), 7.69 (1H, d), 7.65 (1H, d); *m/z* [APCIMS]: 198.0/200.0 [*M*+*H*]<sup>+</sup>.

**Preparation 3: 6-Trimethylsilanylethynyl-[1,2,4] triazolo[1,5-*a*] pyridine**

- 5 6-Bromo-[1,2,4] triazolo[1,5-*a*] pyridine (5 g, 25.26 mmol, 1 eq) was dissolved in THF (50 ml) and argon bubbled through the solution for 5 min. To this was added copper iodide (0.46 g, 2.53 mmol, 0.1 eq), dichlorobis(triphenyl)phosphine (0.36 g, 0.51 mmol, 0.02 eq), and trimethylsilylacetylene (7.14 ml, 4.96 g, 50.52 mmol, 2 eq). Diisopropylamine (6.78 ml, 5.1 g, 50.52 mmol, 2 eq) was added dropwise to the solution and the resulting deep red suspension
- 10 stirred under argon for 24 h. This was then filtered through celite, washing with an excess of ethyl acetate, and the solvents removed. The residue was then suspended in water (200 ml) and extracted with ethyl acetate (2x200 ml), and the organic layers combined, washed with water and brine (100 ml of each), dried (MgSO<sub>4</sub>), and the solvent removed. Purification by flash chromatography over silica, eluting with 3:1 40-60°C petroleum ether: ethyl acetate afforded the
- 15 product as a pale yellow solid (2.9 g, 53.3%); <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>) δ: 8.72 (1H, s), 8.36 (1H, s), 7.69 (1H, d), 7.54, (1H, d), 0.28 (9H, s); m/z [APCIMS]: 216 [M+H]<sup>+</sup>.

**Preparation 4: 6-Ethynyl-[1,2,4]triazolo[1,5-*a*] pyridine**

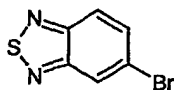
- 20 6-Trimethylsilanylethynyl-[1,2,4]triazolo[1,5-*a*]pyridine (2.9 g, 13.47 mmol, 1 eq) was dissolved in methanol and to this was added potassium carbonate (5.6 g, 40.4 mmol, 3 eq). The suspension was stirred for 2 h and the solvent removed. The residue was suspended in water (100 ml) and extracted with ethyl acetate (2x100 ml). The organic layers were then combined, washed with
- 25 water and brine (50 ml of each), dried (MgSO<sub>4</sub>), and the solvent removed to give a pale orange solid (1.8g, 95%) that was used in the next reaction without further purification; m/z [APCIMS]: 144.1 [M+H]<sup>+</sup>.

**Preparation 5: 6-(3-Chlorophenylethynyl)-[1,2,4]triazolo[1,5-*a*]pyridine**

- 30 A stirred solution of 6-ethynyl-[1,2,4]triazolo[1,5-*a*]pyridine (693 mg, 4.846 mmol) in TMEDA (15ml) and THF (15ml) was degassed with argon. Pd(PPh<sub>3</sub>)<sub>4</sub> (0.253mg, 0.219mmol, 0.05 eq), CuI (100mg, 0.524mmol, 0.1 eq) and 3-chloriodobenzene (2.311g, 9.69mmol, 2eq) were added, and the solution heated at 50°C for 16 h under argon. The solvent was removed *in vacuo* and the
- 35 residue partitioned between ethyl acetate (3 x 70ml) and saturated aq. NaHCO<sub>3</sub> (70ml). The ethyl

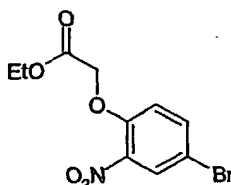
acetate layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to dryness *in vacuo*. Silica gel chromatography, eluting with ethyl acetate/petroleum spirit (4:6), gave the product as a yellow solid (824 mg, 67%); CIMS: 254.1  $[\text{M}+\text{H}]^+$ .

5 **Preparation 6: 5-Bromobenzo[1,2,5]thiadiazole**



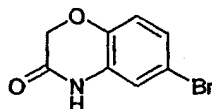
To 4-bromobenzene-1,2-diamine (17 g, 91 mmol) was added thionyl chloride (200 ml). One drop of DMF was added to the reaction mixture. The reaction mixture was heated at reflux under argon at 80°C overnight. The reaction mixture was cooled to room temperature and added portionwise to ice in a large beaker and neutralised with solid sodium bicarbonate. The mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was collected and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure. The title compound was isolated by column chromatography on silica gel eluting with 90% ethyl acetate/10% methanol. (12 g, 62%);  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.61 (1H, dd,  $J=9.2\text{Hz}$ ), 7.82 (1H, d,  $J=9\text{Hz}$ ), 8.16 (1H, s).

**Preparation 7: (4-Bromo-2-nitrophenoxy)acetic acid ethyl ester**



To a stirred solution of 4-bromo-2-nitrophenol (3.71 g, 17.0 mmol, 1.0 eq) in DMF (80 ml) at r.t. was added solid  $\text{K}_2\text{CO}_3$  (4.70 g, 34.0 mmol, 2.0 eq). The mixture was heated at 40°C for 3 h then allowed to cool to r.t. and partitioned between EtOAc and water. The aqueous phase was extracted with more EtOAc and the combined organic phase washed with water, brine and dried over  $\text{MgSO}_4$ . Concentration gave a yellow solid (5.01 g, 97%) which did not require further purification.  $^1\text{H}$  NMR (250 MHz;  $\text{CDCl}_3$ )  $\delta$  8.00 (1H, d), 7.62 (1H, dd), 6.90 (1H, d), 4.76 (H, s), 4.26 (2H, q), 1.29 (3H, t).

**Preparation 8: 6-Bromo-4H-benzo[1,4]oxazin-3-one**

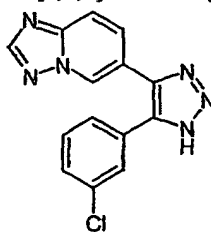


To a stirred solution of (4-bromo-2-nitrophenoxy)acetic acid ethyl ester (4.01 g, 13.2 mmol, 1.0 eq) in glacial acetic acid (70 ml) at r.t. was added iron powder (14.70 g, 264.0 mmol, 20.0 eq).

- The mixture was stirred vigorously at 60°C for 4 h then allowed to cool to r.t. The mixture was filtered through a pad of Kieselguhr, washing through with EtOAc, and the solution evaporated to dryness. The residue was partitioned between saturated aqueous NaHCO<sub>3</sub> solution and EtOAc. The aqueous was extracted with EtOAc and the combined organic phases washed with water, brine and dried over MgSO<sub>4</sub>. Concentration gave the title compound (2.90 g, 97%) as a white solid which did not require purification. <sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>) δ: 10.79 (1H, br.s) 7.09-7.01 (2H, m), 6.91 (1H, d), 4.59 (2H, s).

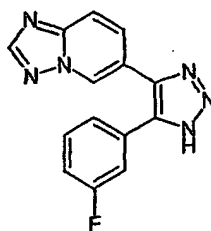
## 10 EXAMPLES

Example 1: 6-[5-(3-Chlorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine

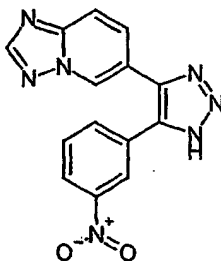


- A stirred solution of 6-(3-chlorophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (Preparation 5) (205 mg, 0.807 mmol) in DMF (1.1 ml) under argon was treated with azidotrimethylsilane (0.32 ml, 2.42 mmol), and heated at 130°C for 19 h. The DMF was removed *in vacuo* and the mixture partitioned between ethyl acetate and brine. The ethyl acetate layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to dryness *in vacuo*. The residue was purified by silica chromatography, eluting with petroleum spirit/ethyl acetate 2:1 → neat ethyl acetate, giving an off-white solid (83mg, 35%); <sup>1</sup>H NMR (250MHz; CDCl<sub>3</sub>) δ: 8.97 (1H, s), 8.42 (1H, s), 7.84 (1H, d), 7.74 (1H, dd), 7.62 (1H, d), 7.46 (3H,m); NH not observed; m/z [ESMS]: 297 [M+H]<sup>+</sup>.

Example 2: 6-[5-(3-Fluorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine



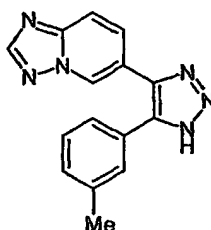
- The title compound was prepared from 6-(3-fluorophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (171mg, 0.722 mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (400MHz; d<sub>6</sub>-DMSO, free base) δ: 15.49 (NH, br.s), 9.03 (1H, s), 8.57 (1H, s), 7.93 (1H, d), 7.70 (1H, d), 7.48-7.27 (4H, m); m/z [ESMS]: 281 [M+H]<sup>+</sup>.

**Example 3: 6-[5-(3-Nitrophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

5 The title compound was prepared from 6-(3-nitrophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (213mg, 0.807mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (400MHz; d<sub>6</sub>-DMSO, free base) δ: 15.74 (NH, br.s), 9.15 (1H, s), 8.59 (1H, s), 8.40 (1H, s), 8.27 (1H, d), 7.95 (2H, br.s), 7.73 (2H, br.s); m/z [ESMS]: 308 [M+H]<sup>+</sup>.

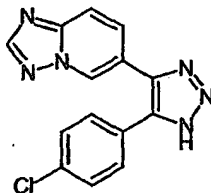
**Example 4: 6-[5-(3-Methylphenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

10



The title compound was prepared from 6-(3-methylphenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (188 mg, 0.805 mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>, free base) δ: 9.16(1H, s), 8.43 (1H, s), 7.79 (2H, d), 7.41-7.28 (4H, m), 2.38 (3H, s); NH not observed; m/z [ESMS]: 277 [M+H]<sup>+</sup>.

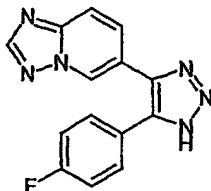
15

**Example 5: 6-[5-(4-Chlorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

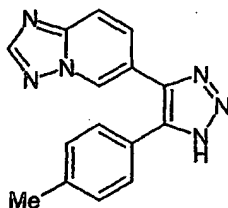
20 The title compound was prepared from 6-(4-chlorophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (102 mg, 0.40 mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (250 MHz; CD<sub>3</sub>OD, free base) δ: 8.83 (1H, s), 8.35 (1H, s), 7.73 (1H, d), 7.69 (1H, d), 7.45 (2H, d), 7.36 (2H, d), NH not observed; [ESMS]: 297 [M+H]<sup>+</sup>.

25

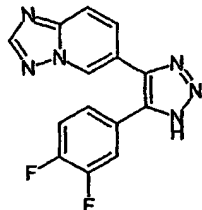


**Example 6: 6-[5-(4-Fluorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

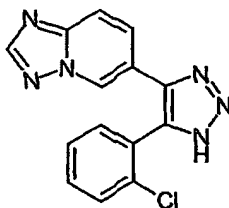
The title compound was prepared from 6-(4-fluorophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (195 mg, 0.821 mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (400MHz; CDCl<sub>3</sub>, free base) δ: 13.45 (NH, br.s), 9.12 (1H, s), 8.44 (1H, s), 7.83 (1H, d), 7.74 (1H, d), 7.57-7.51 (2H, m) 7.17-7.10 (2H, m); m/z [ESMS]: 281 [M+H]<sup>+</sup>.

**Example 7: 6-[5-(4-Methylphenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

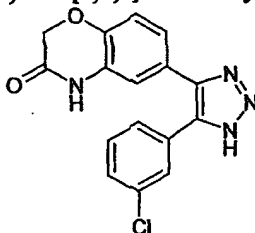
The title compound was prepared from 6-(4-methylphenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (180mg, 0.773mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (400MHz; DMSO, free base) δ: 15.33 (NH, br.s), 8.97 (1H, s), 8.54 (1H, s), 7.91 (1H, d), 7.70 (1H, d), 7.44 (2H, d) 7.27 (2H, br. s), 2.45 (3H, s); m/z [ESMS]: 277 [M+H]<sup>+</sup>.

**Example 8: 6-[5-(3,4-Difluorophenyl)-1H-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-a]pyridine**

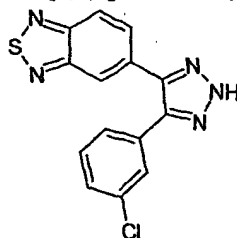
The title compound was prepared from 6-(3,4-difluorophenylethynyl)-[1,2,4]triazolo[1,5-a]pyridine (139mg, 0.545mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>, free base) δ: 9.01 (1H, s), 8.43 (1H, s), 7.83 (1H, d), 7.70 (1H, d), 7.49-7.40 (1H, m), 7.19-7.30 (2H,m), NH not observed; m/z [ESMS]: 299 [M+H]<sup>+</sup>.

**Example 9: 6-[5-(2-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-[1,2,4]triazolo[1,5-*a*]pyridine**

- 5 The title compound was prepared from 6-(2-chlorophenylethynyl)-[1,2,4]triazolo[1,5-*a*]pyridine (189 mg, 0.746 mmol) using a similar procedure to that described for Example 1. <sup>1</sup>H NMR (400 MHz; d<sub>6</sub>-DMSO, free base) δ: 15.63 (1H, br.s), 8.74 (1H, s), 8.51 (1H, s), 7.91 (1H, d), 7.68-7.52 (5H, m), m/z [ESMS]: 297 [M+H]<sup>+</sup>.

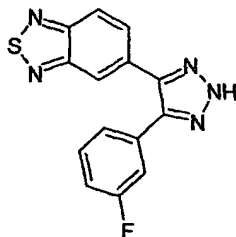
**Example 10: 6-[5-(3-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one**

- To a stirred suspension of 6-(3-chlorophenylethynyl)-4*H*-benzo[1,4]oxazin-3-one (0.311 g, 1.15 mmol, 1.0 eq) in dry DMF (1.5 ml) was added (trimethylsilyl)azide (0.397 g, 3.45 mmol, 3.0 eq). The mixture was degassed with argon for 5 mins and then heated in a sealed tube at 110°C for a total of 72 h. More (trimethylsilyl)azide (0.397 g, 3.45 mmol, 3.0 eq) was added after 24 h. The mixture was allowed to cool then partitioned between water and EtOAc. The aqueous layer was extracted with more EtOAc and the combined organic phase washed with water, brine and dried over MgSO<sub>4</sub>. Concentration gave a solid which was purified by flash column chromatography over silica, eluting with 50%EtOAc-petrol – EtOAc. The product was obtained as a yellow solid
- 15
- 20 (0.063 g, 17%). <sup>1</sup>H NMR (250 MHz; DMSO-*d*<sub>6</sub>) (NMR very broad at r.t) δ: 10.80 (1H, br.s), 7.55-7.35 (4H, m), 7.20-6.90 (3H, m), 4.63 (2H, s), triazole NH not observed; m/z [ESMS]: 327.2 [M+H]<sup>+</sup>.

**Example 11: 5-[5-(3-Chlorophenyl)-2*H*-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole**

Prepared from 5-(3-chlorophenylethynyl)-benzo[1,2,5]thiadiazole using a similar procedure to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.22 (1H, s), 8.01 (1H, d), 7.80 (1H, d), 7.37 (3H, m), 7.17 (1H, t), NH not observed.

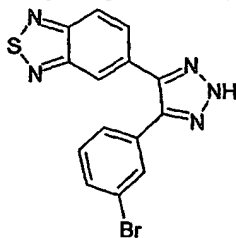
5 **Example 12: 5-[5-(3-Fluorophenyl)-2H-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole**



Prepared from 5-(3-fluorophenylethynyl)-benzo[1,2,5]thiadiazole using a similar procedure to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 8.24 (1H, s), 8.04 (1H, d), 7.84 (1H, d), 7.35 (3H, m), 7.15 (1H, t), NH not observed.

10

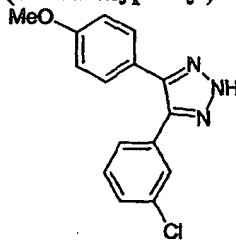
**Example 13: 5-[5-(3-Bromophenyl)-2H-[1,2,3]-triazol-4-yl]-benzo[1,2,5]thiadiazole**



Prepared from 5-(3-bromophenylethynyl)-benzo[1,2,5]thiadiazole using a similar procedure to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 8.24 (1H, s), 8.02 (1H, d), 7.80 (1H, s), 7.56 (1H, d), 7.45 (1H, d), 7.26 (1H, t), NH not observed; m/z [APCIMS]: 358/360 [M+H<sup>+</sup>].

15

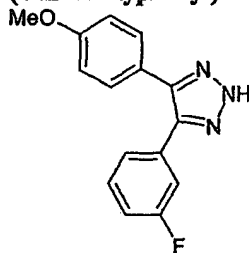
**Example 14: 4-(3-Chlorophenyl)-5-(4-methoxyphenyl)-2H-[1,2,3]triazole**



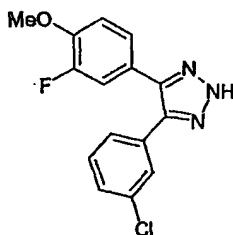
Prepared from 3-(4-methoxyphenylethynyl)chlorobenzene using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.61 (1H, m), 7.46 (3H, m), 7.30 (2H, m), 6.93 (2H, m), 3.84 (3H, s), NH not observed; m/z [APCIMS]: 286.2 [M+H<sup>+</sup>].

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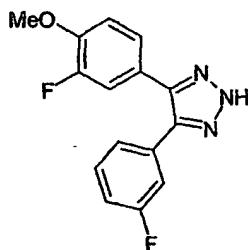
**Example 15: 4-(3-Fluorophenyl)-5-(4-methoxyphenyl)-2H-[1,2,3]triazole**

5 Prepared from 3-(4-methoxyphenylethynyl)fluorobenzene using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): 7.47 (2H, d), 7.35 (3H, m), 6.95 (1H, m), 6.92 (2H, d), 3.85 (3H, s), NH not observed; m/z [APCIMS]: 270.2 [M+H<sup>+</sup>].

**Example 16: 4-(3-Chlorophenyl)-5-(3-fluoro-4-methoxyphenyl)-2H-[1,2,3]triazole**

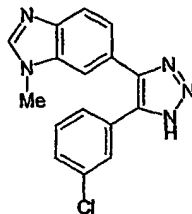
10

Prepared from 3-(3-fluoro-4-methoxyphenylethynyl)fluorobenzene using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.60 (1H, s), 7.37 (5H, m), 6.97 (1H, t), 3.92 (3H, s), NH not observed; m/z [APCIMS]: 304.1 [M+H<sup>+</sup>].

**Example 17: 4-(3-Fluorophenyl)-5-(3-fluoro-4-methoxyphenyl)-2H-[1,2,3]triazole**

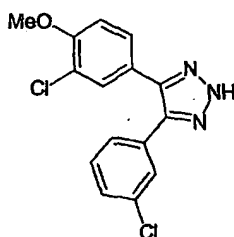
20 Prepared from 3-(3-fluoro-4-methoxyphenylethynyl)fluorobenzene using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.33 (5H, m), 7.09 (1H, m), 6.97 (1H, t), 3.93 (3H, s), NH not observed; m/z [APCIMS]: 288.2 [M+H<sup>+</sup>].

25

**Example 18: 6-[5-(3-Chlorophenyl)-1*H*-[1,2,3]triazol-4-yl]-1-methyl-1*H*-benzimidazole**

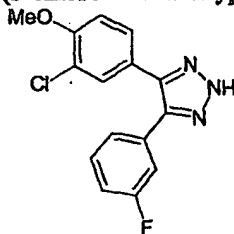
Prepared from 6-(3-chlorophenylethynyl)-1-methyl-1*H*-benzimidazole using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (HCl salt, 400 MHz, MeOH) δ: 9.45 (1H, s), 8.13

5 (1H, s), 7.89 (1H, d), 7.76 (1H, d), 7.55 (1H, s), 7.44-7.37 (3H, m), 4.12 (3H, s), NH not observed. ); m/z [APCIMS]: 267 [M+H<sup>+</sup>].

**Example 19: 4-(3-Chlorophenyl)-5-(3-chloro-4-methoxyphenyl)-2*H*-[1,2,3]triazole**

10

Prepared from 3-(3-chloro-4-methoxyphenylethynyl)chlorobenzene using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.60 (1H, d), 7.50 (1H, d), 7.34 (4H, m), 6.93 (1H, t), 3.92 (3H, s), NH not observed.

**Example 20: 4-(3-Fluorophenyl)-5-(3-chloro-4-methoxyphenyl)-2*H*-[1,2,3]triazole**

20

Prepared from 3-(3-chloro-4-methoxyphenylethynyl)fluorobenzene (500 mg, 1.92 mmol, 1 eq) using a procedure similar to that described for Example 10. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.57 (1H, d), 7.46 (1H, dd), 7.25 (3H, m), 7.1 (1H, t), 6.94 (1H, d), 3.93 (3H, s), NH not observed.

**Biological Data**

The biological activity of the compounds of the invention may be assessed using the following assays:

25

**Method for evaluating ALK5 kinase phosphorylation of smad3**

Basic Flash-Plates (NEN Life Sciences) were coated by pipetting 100 micro liter of 0.1 molar sodium bicarbonate (pH 7.6), containing 150 nanograms of the fusion protein glutathion-S-transferase-smad3/100 micro liter of coating buffer. Plates were covered and incubated at room temperature for 10-24 hours. Then the plates were washed 2 times with 200 micro liter of coating buffer (0.1 molar sodium bicarbonate) and allowed to air dry for 2-4 hours.

For the phosphorylation reaction each well received 90 microliter containing 50 millimolar HEPES buffer (pH 7.4); 5 millimolar  $MgCl_2$ ; 1 millimolar  $CaCl_2$ ; 1 millimolar dithiothreitol; 100 micromolar guanosine triphosphate; 0.5 micro Ci/well gamma<sup>33</sup>P-adenosine triphosphate (NEN Life Sciences) and 400 nanograms of a fusion protein of glutathion-S-transferase at the N-terminal end of the kinase domain of ALK5 (GST-ALK5). Background counts were measured by not adding any GST-ALK5. Inhibitors of ALK5 were evaluated by determining the activity of the enzyme in the presence of various compounds. Plates were incubated for 3 hours at 30°C. After incubation the assay buffer was removed by aspiration and the wells were washed 3 times with 200 microliter cold 10 millimolar sodium pyrophosphate in phosphate buffered saline. The last wash was aspirated and blotted plate dry. Plate was then counted on a Packard TopCount.

**Fluorescence Anisotropy Kinase Binding Assay**

The kinase enzyme, fluorescent ligand and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10x  $K_i$ ) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

The concentration of kinase enzyme should preferably be  $\geq 1 \times K_f$ . The concentration of fluorescent ligand required will depend on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration. A typical protocol is:

All components dissolved in Buffer of final composition 50 mM HEPES, pH 7.5, 1 mM CHAPS, 1 mM DTT, 10 mM  $MgCl_2$  2.5% DMSO.

ALK5 Enzyme concentration: 4 nM

Fluorescent ligand concentration: 1 nM

Test compound concentration: 0.1 nM - 100  $\mu$ M

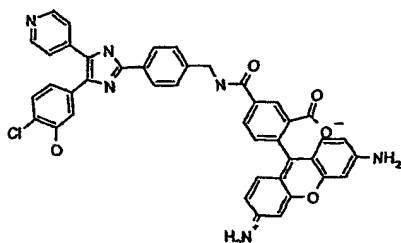
Components incubated in 10  $\mu$ l final volume in LJI HE 384 type B black microtitre plate until equilibrium reached (5-30 mins)

Fluorescence anisotropy read in LJI Acquest.

Definitions:  $K_i$  = dissociation constant for inhibitor binding

$K_f$  = dissociation constant for fluorescent ligand binding

The fluorescent ligand is the following compound:



which is derived from 5-[2-(4-aminomethylphenyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-2-chlorophenol and rhodamine green.

#### 5 Inhibition of Matrix Markers: Northern Blot Protocol

Data confirming activity in the enzyme assay was obtained as follows:

- A498 renal epithelial carcinoma cell lines were obtained from ATCC and grown in EMEM medium supplemented with 10% fetal calf serum, penicillin (5 units/ml) and streptomycin (5ng/ml). A498 cells were grown to near confluence in 100mm dishes, serum-starved for 24 hours, pre-treated with compounds for 4 hours followed by a 10ng/ml addition of TGF-beta1 (R&D Systems, Inc., Minneapolis MN). Cells were exposed to TGF-beta1 for 24 hours. Cellular RNA was extracted by acid phenol/chloroform extraction (Chomczynski and Sacchi, 1987). Ten micrograms of total RNA were resolved by agarose gel electrophoresis and transferred to nylon membrane (GeneScreen, NEN Life Sciences, Boston MA). Membranes were probed with 32P-labeled cDNA probes (Stratagene, La Jolla, CA) for fibronectin mRNA. Membranes were exposed to phosphorimaging plates and bands were visualized and quantified with ImageQuant software (Molecular Dynamics, Sunnyvale, CA).

#### Inhibition of Matrix Markers: Western Blot Protocol

- Data confirming activity in the enzyme assay was obtained as follows:

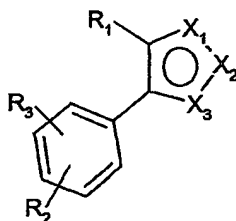
- Cells were grown to near confluence in flasks, starved overnight and treated with TGF-beta and compounds. Cells were washed at 24 or 48 hours after treatment with ice cold phosphate buffered saline, then 500 microliter of 2X loading buffer was added to plate and cells were scraped and collected in microcentrifuge tube. (2X loading buffer: 100 mM Tris-Cl, pH6.8, 4% sodium dodecyl sulfate, 0.2% bromophenol blue, 20% glycerol, 5% beta-mercapto-ethanol). Cells were lysed in tube and vortexed. Sample was boiled for 10 minutes. 20 microliters of sample was loaded on 7.5% polyacrylamide gel (BioRad) and electrophoresed.

- Size fractionated proteins in gel were transferred to nitrocellulose membrane by semidry blotting. Membrane was blocked overnight with 5% powdered milk in phosphate buffer saline (PBS) and 0.05% Tween-20 at 4 degrees C. After 3 washes with PBS/Tween membranes were incubated with primary antibody for 4 hours at room temperature. After three washes with PBS/Tween membrane was incubated with secondary antibody for 1 hour at room temperature. Finally, a signal was visualized with ECL detection kit from Amersham.

- The compounds of this invention generally show ALK5 receptor modulator activity having IC<sub>50</sub> values in the range of 0.0001 to 10 μM.

## Claims:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

- wherein R<sub>1</sub> is naphthyl or phenyl optionally substituted with one or more substituents selected from halo, -O-C<sub>1-6</sub>alkyl, -S-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, -O-(CH<sub>2</sub>)<sub>n</sub>-Ph, -S-(CH<sub>2</sub>)<sub>n</sub>-Ph, cyano, phenyl, and CO<sub>2</sub>R, wherein R is hydrogen or C<sub>1-6</sub>alkyl, and n is 0, 1, 2 or 3; or R<sub>1</sub> is phenyl or pyridyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms, independently selected from N, O and S, and N may be further optionally substituted by C<sub>1-6</sub> alkyl, and wherein the cyclic ring may be optionally substituted by =O;

- R<sub>2</sub> and R<sub>3</sub> are independently selected from H, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, phenyl, NH(CH<sub>2</sub>)<sub>n</sub>-Ph, NH-C<sub>1-6</sub>alkyl, halo, alkoxy, CN, NO<sub>2</sub>, CONHR and SO<sub>2</sub>NHR;

- two of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are N and the other is NR<sub>4</sub> wherein R<sub>4</sub> is hydrogen, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, -(CH<sub>2</sub>)<sub>p</sub>-CN, -(CH<sub>2</sub>)<sub>p</sub>-CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>p</sub>-CONHR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>p</sub>COR<sub>5</sub>, -(CH<sub>2</sub>)<sub>q</sub>(OR<sub>7</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>OR<sub>5</sub>, -(CH<sub>2</sub>)<sub>q</sub>-CH=CH-CN, -(CH<sub>2</sub>)<sub>q</sub>-CH=CH-CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>p</sub>-CH=CH-CONHR<sub>5</sub>R<sub>6</sub>, -(CH<sub>2</sub>)<sub>p</sub>NHCOR<sub>8</sub> or -(CH<sub>2</sub>)<sub>p</sub>NR<sub>9</sub>R<sub>10</sub>;

- R<sub>5</sub> and R<sub>6</sub> are independently hydrogen or C<sub>1-6</sub>alkyl;

R<sub>7</sub> is C<sub>1-6</sub>alkyl;

R<sub>8</sub> is C<sub>1-7</sub>alkyl, or optionally substituted aryl, heteroaryl, arylC<sub>1-6</sub>alkyl or heteroaryl C<sub>1-6</sub>alkyl;

R<sub>9</sub> and R<sub>10</sub> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and arylC<sub>1-6</sub>alkyl;

- p is 0-4; and

q is 1-4.

2. A compound of according to claim 1 wherein R<sup>1</sup> is phenyl optionally substituted by halo, or R<sup>1</sup> is phenyl or pyridyl fused with a 5- to 7-membered aromatic or non-aromatic ring wherein said ring optionally contains up to three heteroatoms, independently selected from N, O and S, and N may be further optionally substituted by C<sub>1-6</sub> alkyl, and wherein the cyclic ring may be optionally substituted by =O.

3. A compound according to Claim 2 wherein R<sub>1</sub> represents 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-chlorophenyl, 3-fluoro-4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R<sub>1</sub> represents benzo[1,2,5]thiadiazolyl, [1,2,4]triazolo[1,5-a]pyridyl, dihydrobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzimidazolyl, C<sub>1-6</sub> alkylbenzimidazolyl, benzo[1,4]oxazinyl-3-one or benzo[1,4]oxazinyl.



4. A compound according to any one of the preceding claims wherein R<sub>2</sub> is positioned *meta* to the point of attachment to the triazole.
5. A compound according to any one of the preceding claims wherein R<sub>2</sub> is halo, C<sub>1-6</sub> alkyl or NO<sub>2</sub>.
6. A compound according to formula (I) as defined in any one of Examples 1 to 20 or a pharmaceutically acceptable salt thereof.
7. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.
8. A compound of formula (I) as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.
9. The use of a compound of formula (I) as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.
10. A method of inhibiting the TGF- $\beta$  signaling pathway in mammals, comprising administering to a mammal, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.
11. A method for treating a disease selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, and restenosis, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.
12. A method for inhibiting matrix formation in mammals, comprising administering to a mammal, a therapeutically effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/13482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D265/36 C07D285/14 C07D249/06 A61K31/41  
 A61P25/28 A61P19/00 A61P3/12 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 40476 A (SMITHKLINE BEECHAM CORPORATION) 23 May 2002 (2002-05-23) page 22 -page 24; claims 1-12	1-12
Y	WO 01 78723 A (SMITHKLINE BEECHAM CORPORATION) 25 October 2001 (2001-10-25) page 1 -page 12	1-12
Y	WO 01 72737 A (SMITHKLINE BEECHAM CORPORATION) 4 October 2001 (2001-10-04) page 20 -page 22; claims 1-12	1-12
Y	WO 01 62756 A (SMITHKLINE BEECHAM CORPORATION) 30 August 2001 (2001-08-30) page 35 -page 36; claims 1-10	1-12
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

3 April 2003

Date of mailing of the international search report

11/04/2003

Name and mailing address of the ISA

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Authorized officer

Kyriakakou, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/13482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 61576 A (SMITHKLINE BEECHAM CORPRATION) 19 October 2000 (2000-10-19) page 24 -page 26; claims 1-12 -----	1-12
Y	WO 00 10563 A (SMITHKLINE BEECHAM CORPRATION) 2 March 2000 (2000-03-02) page 51 -page 62; claims 1-33 -----	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/13482

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/13482

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0240476	A	23-05-2002	AU 1416302 A WO 0240476 A1	27-05-2002 23-05-2002
WO 0178723	A	25-10-2001	AU 5341801 A EP 1274424 A1 WO 0178723 A1	30-10-2001 15-01-2003 25-10-2001
WO 0172737	A	04-10-2001	AU 4257901 A EP 1268465 A1 WO 0172737 A1	08-10-2001 02-01-2003 04-10-2001
WO 0162756	A	30-08-2001	AU 3391801 A CN 1404478 T EP 1257543 A1 WO 0162756 A1 NO 20023953 A	03-09-2001 19-03-2003 20-11-2002 30-08-2001 21-10-2002
WO 0061576	A	19-10-2000	AT 231143 T AU 4798000 A DE 60001229 D1 EP 1169317 A1 JP 2002541253 T WO 0061576 A1 US 6465493 B1	15-02-2003 14-11-2000 20-02-2003 09-01-2002 03-12-2002 19-10-2000 15-10-2002
WO 0010563	A	02-03-2000	CA 2341370 A1 EP 1112070 A1 WO 0010563 A1	02-03-2000 04-07-2001 02-03-2000

Form PCT/ISA/210 (patent family annex) (July 1992)